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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/799,406	03/12/2004	Jian-min Fu	PC27867A	7344

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EXAMINER	
HABTE, KAHSAY	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 10/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/799,406	FU, JIAN-MIN	
	Examiner	Art Unit	
	Kahsay Habte, Ph. D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-15 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-15 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 5/13/2004.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-15 are pending in this application.

Information Disclosure Statement

2. Applicant's Information Disclosure Statement, filed on 5/13/2004 has been acknowledged. Please refer to Applicant's copies of the 1449 submitted herewith.

Claim Objections

3. Claim 4 is objected to because of the recitation of the term "optionally". Note that a pharmaceutically acceptable carrier is required to make a pharmaceutical composition and, thus, a pharmaceutically acceptable carrier is not an optional ingredient.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-6 and 11-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of anxiety and depression (compounds of formula I antagonizing CRF_1 receptor), does not reasonably provide enablement for the treatment of the rest of the diseases recited in claims 11-15. The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to use the invention commensurate in scope with these claims.

A number of factors are relevant to whether undue experimentation would be required to practice the claimed invention, including "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

(1). Breadth of Claims: Claims 5-6 and 11-15 are directed to (1) a method of treating a laundry list of diseases as recited in claim 11, (2) a method of treating any disorder manifestation of CRF in a warm-blooded animal as recited in claim 5, and (3) a method of treating a disorder in a mammal that can be effected or facilitated by antagonizing CRF comprising administering to a mammal a therapeutically effective amount of a compound of any one of claims 1 to 3. The scope of use that applicants intend to claim is very broad. Applicants are claiming the treatment of myriad diseases (e.g. cancer, Alzheimer's disease, Parkinson's disease, stroke, infertility, many type of dementia, etc.) that are different one from the other. In regard to claims 5-6, the scope of use is unknown. There is no standard set of diseases manifesting hypersecretion of CRF or diseases that require the inhibition of CRF receptor.

(2). Direction of Guidance: The amount of direction or guidance is minimal. It is also noted that generic dosage is disclosed, regardless of the nature of the diseases. No guidance appears as to what other diseases are covered in claims 5-6.

(3). State of Prior Art: There is no evidence of record that compounds structurally similar to these pyrrolo[1,2-b]pyridazine compounds or indeed are in use for the treatment e.g. cancer, Alzheimer's disease, Parkinson's disease, stroke, infertility, etc.

(4). Working Examples: There is no biological data for any pyrrolo[1,2-b]pyridazine compounds. The procedures for in vitro and ex vivo CRF_1 receptor binding assays and the assay for measuring the inhibition of CRF stimulated adenylate cyclase activity are described on pages 17-20 of the specification. No results are shown. Only references for in vivo procedures on pages 19-20.

(5). Nature of the Invention and Predictability: The invention is directed to the treatment of various diseases that are linked to CRF receptor. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). CRF are especially unpredictable due to their complex nature.

(6). The Quantity of Experimentation Necessary: Since sufficient teaching and guidance have been provided (see 1-5), one of ordinary skill in the art, even with high degree of skill, would not be able to use all the compounds as claimed without undue experimentation.

(7). The Relative Skill of Those in the Art: The relative skill is extremely very low. Although CRF may be implicated in various diseases, however, its effects are established mainly in treatment of anxiety or depression. Instances of hypersecretion and hyposecretion of CRF are known, each are linked to different sets of disorders. There are at least two subtypes of CRF receptors: CRF_1 and CRF_2. The function of these receptor subtypes in diseases is still currently the subject of research by He et al. (*J. Med. Chem.* (2000), 43:449-456).

Ligands of CRF receptor have been described by Chorvat et al. (*J. Med. Chem.* (2000), 42: 833-848). A CRF_1 antagonist has been described by He et al. (*J. Med. Chem.* (2000), 43:449-456).

At present there is no known drug effective for treatment of all the different classes of diseases, such as any type of neurodegenerative diseases, HIV infection, gastrointestinal diseases, skin disorders, cancer of any kinds etc. etc. as recited in the instant claims.

In regard to the treatment of hair loss, to this day there is no drug that can reverse this process. Hair loss is a normal biological process that affects adults, thus, no one was able to reverse this biological process.

There are myriad of diseases recited in claim 11, but there is no support in the specification to enable this. There is no biological data or working example that directly link the treatment of the diseases recited in the instant claims. Note that claims 11-15 are not tied to CRF receptor.

It is recommended that applicants limit the CRF receptor to CRF type 1 (CRF_1) antagonist for the treatment of anxiety and depression to overcome this rejection.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention:

a. Claim 1 and claims dependent thereon are rejected because the phrase "prodrug thereof" is indefinite. Determining whether a given derivative definitely is or is not a prodrug involves more than routine experimentation. If the derivative is active, open-ended experimentation may be involved to determine for sure whether the compound is a prodrug or whether it is active in its own right (paragraph 2).

b. In claims 5-6, it is recited a method of treating a disorder manifesting hypersecreation of CRF in warm-blooded animal or a method for the treatment of a disorder in a mammal, the treatment of which disorder can be affected or facilitated by antagonizing CRF. The scope of claims 5-6 is unknown. Which diseases are these? Determining whether a given disease responds or does not respond to such mediator will surely involve undue experimentation. Suppose that a given inhibitor X when administered to a patient with Disease D does not obtain a response. Does one then conclude that Disease D does not fall within this claim? Keep in mind that:

A. It may be that the next patient will respond. It is quite common for pharmaceuticals to work only with some people, not all. Thus, how many need to be tested?

B. It may be that the wrong dosage or dosage regimen was employed. It is quite common for pharmaceuticals to work at one dosage, but not at another which is significantly higher or lower. Furthermore, the dosage regimen may be vital --- should the drug be given e.g. once a day, or four times in divided dosages? Thus, how many dosages and dosage regimens must be tried before one is certain that this pharmaceutical won't affect Disease D?

C. It may be that X simply isn't potent enough for Disease D, but that another inhibitor Y is potent enough, so that D really does fall within the claim. Thus, how many different mediators must be tried before one concludes that D doesn't fall within the claim?

D. Conversely, if D responds to Y but not to X, can one really conclude that D falls within the claim? It may be that the X result is giving the accurate answer, and that the success of Y arises from some other unknown property which Y is capable of. Thus, when mixed results are obtained, how many more pharmaceuticals need be tested?

E. Finally, suppose that X really will work, but only when combined with Z. There are for example, agents in the antiviral and anticancer technology which are not themselves effective, but the disease will respond when the agents are combined with something else.

F. In addition, literally speaking, any disorder can be treated with any drug, although the treatment might not be successful. Assuming that "successful treatment"

is what is intended, what criterion is to be used? If one person in 10 responds to a given drug, does that mean that the disease is treatable? One in 100? 1,000? 10,000?

As a result, determining the true scope of the claim will involve extensive and potentially open-ended research. Without it, one skilled in the art cannot determine the actual scope of the claim. Hence, the claim is indefinite.

c. In claim 11, the phrase "A method of treating ....hair loss", is not clear. Hair loss is a normal biological process, but not a disorder. Is a bold person considered a sick person? As far as we know, hair growth or hair loss is a natural biological process that can't be reversed. The same problem appears in claim 14.

Conclusion

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kahsay Habte, Ph. D. whose telephone number is (571)-272-0667. The examiner can normally be reached on M-F (9.00- 5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Wilson can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Kahsay Habte, Ph. D.
Examiner
Art Unit 1624

KH
October 11, 2005